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Cancer Prevention Trials in China and Finland

Philip R. Taylor, MD, ScD, Sanford Dawsey, MD,
and Demetrius Albanes, MD

Abstract

*Intervention studies are now viewed as a useful and necessary approach to understanding the relation between nutrition and cancer. Over 20 such studies have been initiated in the past 7 years. Foreign countries may be an attractive site for such investigations, mainly because of desirable population characteristics such as unusually high rates of the cancer being studied, low dietary intake of potential chemopreventive nutrients, stability of the population, and high compliance, and also because of favorable logistical aspects including existing medical, social, or governmental structures that facilitate delivery of the intervention, ongoing cancer registries for endpoint determination, and reduced cost. The three basic elements of an intervention trial, identification and recruitment of a study population, delivery of the intervention and assessment of compliance, and ascertainment of endpoints, are the same in a foreign country as in the United States, but there are a number of special considerations, most notably communication difficulties due to language differences and distance between collaborators, which complicate foreign trials both before and during implementation. The basic elements and status of ongoing trials in China and Finland are presented. *Ann Epidemiol* 1990;1:195-203.*

KEY WORDS: Cancer, prevention, nutrition, trials, China, Finland

INTRODUCTION

In the 1970s, congressional hearings focused on our understanding of the health effects of nutrition. As an outgrowth of that inquiry, the Office of Technology Assessment of the US Congress commissioned Sir Richard Doll and Richard Peto to write a report, "The Causes of Cancer," in which they estimated that perhaps 35% of all cancer deaths were due to diet (1). Also as a result of those congressional hearings, the National Cancer Institute commissioned the National Research Council to conduct a comprehensive study of the relation of diet and nutrition to cancer (2). With these two documents as a stimulus, the National Cancer Institute (NCI) developed a program of cancer prevention focusing on diet and emphasizing clinical trials. Clinical prevention trials were viewed as the most expeditious approach to gaining specific, definitive information on the diet and cancer relation (3). As a result of this strategy, more than 20 prevention trials have been funded by the NCI over the past 7 years. A brief summary of these intervention studies by target site, target population, and inhibitory agents is shown in Table 1 (4). These studies include pilot efforts and studies of precursor lesions as well as studies of cancer itself. Five of the studies are being conducted in foreign countries. In this paper we discuss considerations for conducting cancer prevention trials in foreign countries.

From Cancer Prevention Studies Branch, Cancer Prevention Research Program, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health, Bethesda, MD.

Address for reprints: Philip R. Taylor, MD, ScD, National Cancer Institute, National Institutes of Health, EPN, Rm. 211, Bethesda, MD 20892.

Received April 11, 1990; revised May 16, 1990.

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1047-2797/90/\$03.50

TABLE 1 Current NCI-funded chemoprevention intervention studies*

Target site	Target group	Inhibitory agents	Organization
All	Physicians	Aspirin, beta-carotene	Harvard Medical School
Breast	Prior breast cancer	4-hydroxyphenyl retinamide (4-HPR)	Instituto Nazionale Tumori
Cervix	Dysplasia	Beta-trans retinoic acid	University of Arizona
Cervix	Dysplasia	Folic acid	University of Washington
Colon	Previous colon adenoma	Beta-carotene, vitamin C, vitamin E	Dartmouth College
Colon	Previous adenoma	Calcium	Dartmouth College
Colon	Previous adenoma	Wheat bran, calcium carbonate	University of Arizona
Colon	Previous adenoma	Piroxicam	University of Arizona
Colon	Previous adenoma	Calcium	University of Minnesota
Esophagus	High-risk area	Multiple vitamins & minerals, beta-carotene	China, NCI
Esophagus	Dysplasia, high-risk area	Multiple vitamins & minerals, beta-carotene	China, NCI
Lung	Men, exposed to asbestos	Beta-carotene, retinol	University of Texas, Tyler
Lung	Smokers	13-cis retinoic acid	M.D. Anderson Cancer Center
Lung	Smokers	Alpha-tocopherol, beta-carotene	Finland, NCI
Lung	Smokers and/or asbestos exposure	Beta-carotene, retinol	University of Washington
Oral cavity	Leukoplakia	13-cis retinoic acid, +/- beta-carotene	M.D. Anderson Cancer Center
Skin	Albinos in Tanzania	Beta-carotene	Muhimbili Medical Center
Skin	Previous SCC or BCC	Beta-carotene	Dartmouth College
Skin	Previous SCC or BCC	Retinol, 13-cis retinoic acid	University of Arizona
Skin	Actinic keratosis	Retinol	University of Arizona
Skin	Previous BCC	13-cis retinoic acid	NCI

* From Dr. Marjorie Perloff, Chemoprevention Branch, NCI, May 1990.
SCC = squamous cell carcinoma; BCC = basal cell carcinoma.

REASONS FOR CONDUCTING FOREIGN CANCER PREVENTION TRIALS

The major attraction of a foreign country for conducting a cancer prevention trial is usually the characteristics of a specific foreign population. One of the most important aspects of any intervention study is its size, meaning both the number of subjects and the duration of intervention needed to answer the question being asked. To keep the size of a study manageable, it is often desirable to perform the intervention where the rate of the disease being studied is highest. This is an especially important fiscal and logistical consideration for cancer prevention trials because trials with cancer incidence as an endpoint typically require thousands of subjects. For example, an intervention with 90% power to observe a 25% reduction in cancer incidence over 5 years in a population with a 1% annual incidence rate (a rate higher than that of any single cancer site in the general population in this country) would require nearly 10,000 subjects, assuming perfect compliance and no dropouts. Thus, a high incidence rate of the cancer to be studied is often of primary importance in choosing to study a foreign

population. General stability of a population and likely compliance are other population characteristics that merit attention. It is also necessary that the characteristics of the population are consistent with the hypothesis being studied. Nutritional supplementation, for example, may be a more credible intervention in a nutritionally depleted population rather than in one with adequate nutriture.

Logistical considerations are also important in deciding to initiate a study abroad. Existing elements in the medical, social, or governmental structure may be natural conduits for the delivery of an intervention. Endpoint determination may be facilitated by registry systems that are already functioning. Use of such pre-existing systems, differences in labor costs, and other fiscal factors may combine to make a foreign country attractive from a logistical and cost point of view.

REQUIREMENTS FOR CONDUCTING FOREIGN TRIALS

The basic elements that must be considered in conducting cancer prevention trials are the same whether the trials will be carried out in a foreign country or in this country. Once a basic hypothesis and study plan have been developed, there are three main elements essential to the success of any prevention trial. These elements are: (1) identification and recruitment of a study population, (2) delivery of the intervention and assessment of compliance, and (3) ascertainment of endpoints. Special attention, however, needs to be paid to some aspects in foreign trials.

There may be additional prerequisites associated with foreign trials. Governmental approval is invariably required in conducting foreign studies, typically necessitating permission at multiple levels. Collaborators must be identified and working relationships developed, including some understanding of the talents and expected roles of major participants. Resources, both human and monetary, must be found. Pilot or feasibility studies, always a good idea in the initial stages of a scientific effort, become mandatory to ensure the technical and logistical feasibility of implementing the essential elements of the trial, especially when there are significantly different social, cultural, and economic circumstances between the two collaborating countries.

There are also other factors requiring consideration during the implementation phase of cancer prevention trials which mainly affect foreign trials. These include bilingual communication, collaborative decisionmaking over long distances, travel and fiscal restrictions, and other considerations. Foreign trials almost always involve verbal and written bilingual communication, with inevitable misunderstandings. It is usually necessary to use bilingual study forms, manuals, and data-file documentation. Distances between countries commonly make collaborative decisionmaking and data management a slow process. Budgetary limits restrict extensive travel for federal employees and severely limit the number of site visits that US investigators can make to foreign study sites. Operating budgets for such studies must be projected for years in advance and are subject to changes in exchange rates and inflation. Other considerations that occasionally occur include ethical questions arising from cultural differences and standards and political questions such as the effects of political shifts in either of the collaborating countries during long-term trials.

GENERAL BACKGROUND

We would now like to illustrate the basic elements of a foreign cancer prevention trial, using examples of ongoing trials in China and Finland.

China

Two double-blind, randomized, controlled nutrition intervention studies to prevent esophageal cancer have been initiated in Linxian, China (5). These studies are being conducted collaboratively between the Cancer Institute of the Chinese Academy of Medical Sciences and the NCI of the United States. For both trials, study subjects were 40 to 69 years old at the onset of the study and will be followed for the development of esophageal cancer for 5 to 6 years during intervention and for 5 years after intervention. The first trial, termed the Dysplasia Trial, is limited to 3393 subjects from three communes in northern Linxian with cytologically demonstrated dysplasia who are at especially high risk for esophageal cancer. This trial uses a simple two-arm design and provides participants either with two multivitamin/mineral tablets (Centrum® tablets, provided by Lederle Laboratories, Inc, Pearl River, NY) each containing from 1.0 to 1.5 times the US Recommended Daily Allowances for 25 different vitamins and minerals, and one 15-mg beta-carotene capsule (provided by Hoffmann-LaRoche, Inc, Nutley, NJ) daily or with matching placebos. The second study, the General Population Trial, includes 30,258 subjects from four communes in northern Linxian and uses a fractional factorial design to test the effect of four different multiple vitamin/mineral factors, including retinol/zinc (factor A); riboflavin/niacin (factor B); ascorbic acid/molybdenum (factor C); and selenium/alpha-tocopherol/beta-carotene (factor D).

Finland

The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study (ATBC Study) is being conducted collaboratively by the National Public Health Institute of Finland and the NCI of the US (6). This trial is investigating the efficacy of daily oral alpha-tocopherol (vitamin E, 50 mg) or beta-carotene (20 mg), or both, in preventing lung cancer among 50- to 69-year-old male cigarette smokers. The study is double blind and has a randomized 2×2 factorial design. Over 29,000 men have been randomized and will be followed up for 5 to 8 years.

IDENTIFICATION AND RECRUITMENT OF A STUDY POPULATION

China

The highest worldwide incidence and mortality for cancer of the esophagus occurs in the People's Republic of China. A nationwide survey of mortality conducted there from 1973 to 1975 identified esophageal cancer as the second leading cause of cancer death, accounting for 27% of all cancer deaths in men and 20% in women (7). In this survey, the highest esophageal mortality rates occurred in northern Linxian, Henan Province. A comparison of age-adjusted esophageal cancer mortality rates in northern Linxian, China, and the United States is shown in Table 2 (8). The northern Linxian rates are 150-fold higher and China's overall rates are tenfold higher than the esophageal cancer mortality rates for US whites. These high rates made Linxian a very promising place to conduct an intervention study.

Chinese scientists have been investigating the potential causes of esophageal cancer in Linxian and other areas of China for many years (9-17). The Cancer Institute of the Chinese Academy of Medical Sciences established a field station in Linxian 30 years ago. These studies have provided a series of clues to causes, but have not yet identified a specific carcinogen responsible for the elevated rates. Leading clues include: multiple nutrient deficiencies, particularly riboflavin, vitamins A and C, zinc,

TABLE 2 Esophageal cancer mortality rates in Linxian among adults 40 to 69 years old*

Area and population	Annual age-adjusted rate per 100,000
Total Linxian County	470
Linxian's northern communes	760
With dysplasia	1775
Without dysplasia	510
China	56
US whites	5
US blacks	19

* From Blot and Li (8).

and molybdenum; consumption of pickled vegetables and moldy foods, some of which have been shown to be mutagenic; silica contamination of millet; ingestion of foods with high levels of nitrosamines; endogenous production of nitrosamines facilitated by esophageal fungal infections or other factors; and physical trauma from drinking excessively hot tea. The evidence that multiple nutrient deficiencies may contribute significantly to the elevated rates made this area particularly favorable for a clinical trial using supplementation with vitamins and minerals.

The political structure of rural China has been relatively uniform for several decades. The primary political unit is the commune. Communes are, in turn, divided into production brigades, which are subdivided into production teams. Each commune has organized political and public health structures. The health needs of each commune are served by a commune hospital, several doctors, and a group of barefoot doctors. The existing system has been extremely well suited to organizing screening efforts, publicizing intervention activities, and encouraging participation. The pretrial screening process was illustrative of the ability of the Chinese public health officials to organize mass campaigns. Thirteen-member screening teams composed of doctors, interviewers, nurse-phlebotomists, laboratory technicians, and a team manager were organized and trained (5). These teams were mobile and conducted their screening evaluations in different villages each day. Subjects were contacted prior to screening and instructed to report fasting early in the morning on a specified day. After the subjects checked in, height and weight were measured, a blood sample was collected, an interview was completed, and a brief physical examination was performed. Each team completed screening activities daily on 60 to 70 subjects. With three to seven teams using these procedures and working 6 to 7 d/week, 3400 subjects were recruited and screened in about 1 month for the Dysplasia Trial and nearly 30,000 subjects were recruited and screened in just over 3 months for the General Population Trial.

Finland

Nationwide male lung cancer rates in Finland are the highest in the world (18). Available national rates are shown in Table 3 for comparison. Within Finland, rates are generally highest in the south and east and, as for many countries, in urban areas. These high rates, which have been attributed to cigarette smoking, made Finland a desirable target for a lung cancer prevention strategy. From a nutritional viewpoint, Finland has low selenium levels in its soil and consequent low dietary intake and serum levels of this potential chemopreventive agent (19). Selenium supplementation was being considered at the time that the intervention study was being planned for

TABLE 3 Age-standardized national lung cancer rates for males*†

County	Age-standardized rate per 100,000
Finland	74.6
United Kingdom, England, Wales	72.0
Canada	61.3
German Democratic Republic	58.9
Hong Kong	58.3
Denmark	56.5
Netherlands Antilles	35.5
Norway	30.9
Sweden	25.3
Iceland	24.7
Costa Rica	17.8
Martinique	11.1

* Years for which rates are shown vary by country from 1973 to 1982; however, most are from 1978 to 1982.

† From Muir and associates (18).

Finland, but a public health policy decision was made to add selenium to fertilizers to increase soil and thereby food selenium levels, and trial nutrients were limited to alpha-tocopherol and beta-carotene (20). Fresh fruit and vegetable intakes have traditionally been low for a variety of reasons, and relatively low intake (around 2 mg/d) and serum levels (28.6 $\mu\text{g/dL}$) of beta-carotene were observed in a recent pilot study of Finnish males (21). Though the numerous nutritional deficiencies seen in China were not observed in Finland, a nutritional intervention was still suggested.

Favorable logistical attributes were also important in deciding to conduct a cancer prevention trial in Finland. Tuberculosis was a common disease in Finland prior to the Second World War. Now the disease is rare, but a separate tuberculosis organizational structure still exists. The country had been divided into Tuberculosis Sanatory Areas, and each area had one or more outpatient clinics. In addition to patient treatment, high-risk groups, defined by smoking habits, age, sex, and occupation, were under continued annual surveillance. Computerized information concerning the smoking habits of the population was available for the southern and southwestern Tuberculosis Sanatory Areas. The existence of this organizational structure with its clinics and data bases greatly facilitated the process of identifying, recruiting, screening, and following subjects for the intervention study.

DELIVERY OF THE INTERVENTION AND ASSESSMENT OF COMPLIANCE

China

A detailed pill delivery system was established in China, with numerous quality control steps built in. Following randomization, pill distribution logs were printed at the study data management center in the United States and sent to Linxian. Labels for pill bottles were specially designed, each with two coded pull-off tabs. One tab is removed from the bottle and affixed to the pill distribution log at the central distribution point in Linxian where a separate bag of bottles for each barefoot doctor is prepared monthly for distribution. The second tab is removed by the barefoot doctor at the time of his monthly delivery of pills to subjects, and is affixed to a second pill

distribution log kept by the barefoot doctor. At the time of his monthly contact with the subject, the barefoot doctor delivers the new supply of pills, retrieves the bottles from the previous month, and counts and records any remaining pills. Though subject migration from the area has been minimal, most who have migrated continue to receive their new supply of pills and return their old supply using specially designed mailers.

Compliance is monitored by monthly pill counts on all subjects and by quarterly biochemical assessment of blood samples taken from a random sample of study subjects. Pill counts show that more than 90% of subjects are taking more than 90% of their pills. Blood biochemical measures also suggest high compliance. Median plasma levels of beta-carotene during the first year of the General Population Trial, for example, were from 6 to 25 times higher in subjects receiving beta-carotene than in subjects who did not receive beta-carotene. The existing health care system in rural China with its extensive system of barefoot doctors is a unique and invaluable structure upon which we have established our intervention delivery and compliance assessment. This system and the frequent contact with subjects built into the study are probably the main reasons for our observed high rate of compliance.

Finland

The pill delivery system used in the trial in Finland was designed for participant convenience. Wallet-size, calendar blister packs containing a 4-month supply of daily capsules are distributed during each of the three clinic visits each year. Beta-carotene or vitamin E, or both, or a placebo are contained in a single capsule. Each capsule is covered with its own plastic blister marked with the day of the week to facilitate a subjects' memory. Compliance is determined by counting capsules remaining in wallet packs at each clinic visit and by biochemical assessment on blood samples collected at the time of the clinic visits on a random sample of several hundred subjects annually. Pill counts indicate that 94% of subjects are taking more than 90% of their pills. Plasma beta-carotene levels have been significantly higher in persons receiving beta-carotene compared to those not receiving beta-carotene.

ASCERTAINING ENDPOINTS

China

Initial identification of subjects suspected of having cancer usually comes from the barefoot doctor following his monthly visit. During this monthly visit he inquires about symptoms, particularly dysphagia, and any hospitalizations or diagnoses made. These reports are supplemented by cross-checking with the Linxian cancer registry, in place since 1959. At the beginning of the prevention trials, 25% of diagnoses in Linxian were based on histology, 20% on cytology, 40% on x-ray, and 15% on clinical history. Because of increased efforts to encourage any subject with symptoms to have an endoscopic examination, we now estimate that nearly 80% of cancer diagnoses are based on histology. Diagnostic assessment has been further improved by having the diagnostic slides and x-rays for all cancer cases reviewed by an international endpoints review committee composed of both Chinese and American experts in pathology, cytology, and radiology. It is anticipated that nearly 2000 cancers will be diagnosed among trial participants by the end of pill delivery.

Finland

Initial case identification in the ATBC Study routinely occurs at the time of follow-up clinic visits when study nurses learn of a cancer diagnosis. This prompts a search of medical records to confirm the diagnosis and obtain additional information. A nationwide Finnish Cancer Registry system, in place since 1952, is an invaluable adjunct to the clinic and medical record reports. The case ascertainment in this Registry is based on personal identification numbers and the Registry is reported to be nearly 100% complete. Diagnostic materials for cases can be collected and revised by a central board of Registry pathologists. The Registry, with its virtually complete coverage of cancer and the availability of central re-review, is an invaluable aid for a cancer prevention trial.

STATUS OF PREVENTION TRIALS

China

Subjects were identified for the Dysplasia Trial during a mass screening campaign using balloon cytology in November of 1983. Prevalent cases of esophageal or stomach cancer diagnosed during this screening were excluded from the trial. Questionnaires, blood collections, and physical examinations were conducted in the Fall of 1984, and in January 1985, 520 subjects participated in a baseline endoscopic examination. Distribution of active agents began in May 1985. In October 1987, 30 months after pill distribution was initiated, balloon cytologic examinations were again performed, and 2826 of the original 3393 subjects participated. In November 1987, endoscopic examinations were performed on 851 subjects. As of October 1989, subjects had completed 4½ years of intervention. Current plans call for an extension of the intervention to a full 6 years, until April 1991, with repeat balloon cytology and endoscopic examinations at the end of this period. Screening of subjects (questionnaires, blood collections, and physical examinations) for participation in the General Population Trial was conducted in the Spring of 1985 and distribution of intervention agents commenced in March 1986. As of October 1989, approximately 3½ years of the intervention had been finished with completion of the full 5 years expected at the end of February 1991. For both trials, follow-up of all subjects for incident esophageal cancer cases will continue for 5 years after the intervention is completed.

Finland

Recruitment for the ATBC Study took place between 1985 and 1988. The trial will end in 1993 after an average follow-up of over 6 years. Prevalent cases of lung cancer, diagnosed by the baseline screening chest x-ray, were excluded before entry into the trial. Repeat x-rays are being obtained on all subjects at visits 7 and 14 (i.e., after 2½ and 4½ years of intervention), and a final x-ray will be taken at the conclusion of the intervention.

SUMMARY

Large nutrition intervention studies are now being conducted in foreign countries to try to prevent cancer. Though these studies have not yet been completed, the progress to date demonstrates both the feasibility of such efforts and the potential importance of the results in the development of our overall cancer prevention strategy.

We gratefully acknowledge the contributions of our collaborators in these studies, including Drs. Li Bing and Li Jun-Yao, Principal Investigators in China; Drs. Jussi Huttunen and Olli Heinonen, Principal Investigators in Finland; and Dr. William J. Blot, Co-Principal Investigator for the China studies at the National Cancer Institute.

Presented at the annual meeting of the American College of Epidemiology, Washington, DC, October 5, 1989.

REFERENCES

1. Doll R, Peto R. The causes of cancer: Qualitative estimates of available risks of cancer in the United States today, *J Natl Cancer Inst.* 1981;58:825-32.
2. National Academy of Sciences, Committee on Diet, Nutrition and Cancer. *Diet, Nutrition and Cancer.* Washington, DC: National Academy Press; 1982.
3. DeWys WD, Greenwald P. Clinical trials: A recent emphasis in the Prevention Program of the National Cancer Institute, *Semin Oncol.* 1983;10:360-4.
4. Bertram JS, Kolonel LN, Meyskens FL Jr. Rationale and strategies for chemoprevention of cancer in humans, *Cancer Res.* 1987;47:3012-31.
5. Li JY, Taylor PR, Li GY, et al. Intervention studies in Linxian, China—an update, *J Nutr Growth Cancer* 1986;3:199-206.
6. Albanes D, Virtamo J, Rautalahti M, Pikkarainen J, Taylor RR, Heinonen OP. Pilot study—the U.S.-Finland lung cancer prevention trial, *J Nutr Growth Cancer* 1986;3:207-14.
7. Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD. Atlas of cancer mortality in the People's Republic of China. Shanghai: China Map Press; 1979.
8. Blot WJ, Li JY. Some considerations in the design of a nutrition intervention trial in Linxian, People's Republic of China, *NCI Monogr.* 1985;69:29-34.
9. Munoz N, Crespi M, Grassi A, Wang GQ, Shen Q, Li ZC. Precursor lesions of esophageal cancer in high-risk populations in Iran and China, *Lancet.* 1982;1:876-9.
10. Li JY. The epidemiology of esophageal cancer in China, *NCI Monogr.* 1981;62:113-20.
11. Yang CS. Research on esophageal cancer in China: A review, *Cancer Res.* 1980;40:2633-44.
12. Coordinating Group for Research on the Etiology of Esophageal Cancer in North China. The epidemiology and etiology of esophageal cancer in North China: A preliminary report, *Chin Med J.* 1975;1:167-77.
13. Yang CS, Miao Y, Yang W, et al. Diet and vitamin nutrition of the high esophageal cancer risk population in Linxian, China, *Nutr Cancer.* 1982;4:154-64.
14. O'Neill C, Pan QQ, Clark G, et al. Silica fragments from millet bran in mucosa surrounding esophageal tumors in patients in North China, *Lancet.* 1982;1:1202-6.
15. Li MH. Studies of potential carcinogens in the diet of individuals of high risk for esophageal cancer. In: Marks PA, ed. *Cancer Research in the PRC and USA.* New York: Grune & Stratton; 1981:131-6.
16. Lu SH, Camus AM, Tomatis L, Bartsch H. Mutagenicity of extracts of pickled vegetables collected in Linshien county, a high-incidence area for esophageal cancer in Northern China, *J Natl Cancer Inst.* 1981;6:33-6.
17. Li JY, Ershow AG, Chen ZJ, et al. A case-control study of cancer of the esophagus and gastric cardia in Linxian, *Int J Cancer.* 1989;43:755-61.
18. Muir C, Warehouse J, Mack T, Powell J, Whelan S, eds. *Cancer Incidence in Five Continents.* V. Lyon: International Agency for Research on Cancer; 1987:868-9.
19. Alfthan G. Longitudinal study on the selenium status of healthy adults in Finland during 1975-1984, *Nutr Res.* 1988;8:467-76.
20. Varo P, Alfthan G, Ekholm P, Aro A, Koivistoinen P. Selenium intake and serum selenium in Finland: Effects of soil fertilization with selenium, *Am J Clin Nutr.* 1988;48:324-9.
21. Albanes D, Virtamo J, Rautalahti M, Haukka J, Gref CG, Heinonen OP. Serum beta-carotene during and after beta-carotene supplementation. (In review)